REMARKS

Status of the Claims

Claims 1, 3-7 and 9-12 are pending in the application. Claims 2 and 8 were canceled. Claims 1, 3-7 and 9-12 are rejected. Claims 1, 4, 7 and 10 are amended. Claims 3 and 9 are canceled.

The 35 U.S.C. §112, First paragraph Rejection

Amended claims 7 and 9-12 stand rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement since they contain subject matter which was not described in the specification to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention for the same reasons already set forth in the previous Office Action mailed on 11/5/03 (pages 3-7). Applicants respectfully traverse this rejection.

Claim 9 is canceled and Claim 7 is amended to incorporate the limitations of claim 9. Claim 10 is amended to change its dependency. Amended claim 7 now recites a method of increasing targeting specificity to target cells and reducing the transgene expression in non-target cells by adenoviral vector which comprises the step of contacting target cells with an adenoviral vector comprising of targeting component and a tissue-specific promoter. The targeting component further comprises a bi-specific antibody

conjugate linking a Fab fragment of an anti-Ad5 knob antibody with an anti-angiotensin converting enzyme antibody, where the angiotensin converting enzyme molecule is expressed on the target cells. The tissue specific promoter in this adenoviral vector drives the expression of a transgene carried by the vector in the target cells. Such an adenoviral vector has increased targeting specificity to the target cells and results in reduced transgene expression in non-target cells compared to adenoviral vector without the targeting component and the tissue-specific promoter.

The Examiner finds the Applicants earlier arguments unpersuasive and contends that the sole purpose for a method of gene delivery by adenoviral vector as claimed by the invention is to obtain therapeutic effects *in vivo*, particularly for treating pulmonary vascular diseases (Pages 6-9). Applicants respond by stating that the subject matter and scope of the invention are defined by the claims. The amended claim 7 now clearly recites a method of increasing targeting specificity to target cells and reducing transgene expression in non-target cells. Therefore, the Applicants reiterate that the claim does not recite a method of gene delivery nor does it claim a method of obtaining therapeutic effects in vivo. The method is intended to improve the prospects of gene therapy by addressing the limitations of gene therapy (page 34, lines 17-21).

Additionally, the Examiner points out several items that lack sufficient guidance in the instant specification, thereby requiring undue experimentation for one skilled in the art to make and use the method as

claimed. Firstly, the Examiner states that the claims encompassing the method of gene delivery by adenoviral vector are broad.

In response to this statement of the Examiner, the Applicant respectfully notes that the amended claims are clearly enabled by the detailed description and data presented in the specification. The example 5 of the present invention assesses the utility of combining transductional and transcriptional targeting approaches to pulmonary endothelium. Further, the specification clearly teaches that the use of such an adenoviral vector significantly enhances transgene expression in target cells while the transgene expression in non-target cells is significantly reduced (Figures 3-5; page 29, line 6 to page 30, line 16; page 31, lines 16-21). Further, the specification also compares the tail vein and left ventricle as routes of injecting the vector and teaches that the distribution of transgene expression was similar by the two approaches, except that the left ventricular approach also led to higher expression of transgene in the heart (page 30, lines 17 to page 31, line 4; Figure 4). Additionally, although this method of improving the adenoviral vector targeting to pulmonary endothelium is novel, the methods of administration of adenoviral vector, dosages, etc is standard and well known in the art. Hence, one of skill in the art, given the teachings of the present invention, would not be forced into undue experimentation to practice the claimed invention.

Secondly, while referring to the state and unpredictability of the art, the Examiner cites **Romano et al**. (Stem cells 18:19-39, 2000) as stating that the effectiveness of gene therapy programs was still questioned and that despite the

significant achievements reported in vector design, it was not possible to predict what extent gene therapeutic interventions would be effective and in what time frame.

The Applicants respectfully disagree with the Examiner's application of this broad statement of uncertainity of the effectiveness of gene therapy programs to the Applicants' invention. Gene therapy is a relatively new field and the efficacy of this depends on vector and delivery vehicle design. Hence, if the vectors and delivery vehicles improve, so will the efficacy. Applicants' invention has shown significant improvement in specific targeting after modifying the conventionally used adenoviral vectors by combining transductional and transcriptional approaches, which in itself is a significant breakthrough and hence, the aforementioned statement of gene therapy cannot be applied to this case.

Further, while citing **West et al.**, (Chest 119:613-617, 2001), the Examiner states that the success of gene delivery and transcription has been variable in humans since in general, the level of expression of transgene appears to be low. Applicants respond by noting that even assuming *arguendo* that this is true generally this is not the case with the Applicants invention. Figure 6 in the Applicants specification shows the distribution of transgene expression within different organs. The specification teaches that positive signal was detected in small pulmonary vessels, alveolar capillaries, hepatocytes and spleen of rats that received AdCMVCEA/Fab-9B9 combination (Figures 6A, 6C and 6E, page 32, lines 17-21). As opposed to this, transgene expression was detected in 50% of

the aleveolar walls and no signal was detected in livers and spleens of rats that received AdfltCEA/Fab-9B9 combination (Figures 6B, 6D, 6F, page 32, line 21-page 33, line 6). Hence, the Applicants' specification clearly demonstrates increased transgene expression in specific target cells.

Finally, while referring to the lack of direction or guidance presented, the Examiner states that the present disclosure fails to provide any evidence indicating that any therapeutic effect has been achieved *in vivo*. Applicants contend that the present invention is directed towards improving gene therapy and does not make claims towards obtaining therapeutic effects *in vivo*. However, one with skill in the art will be able to apply the teachings of this invention in order to obtain therapeutic effects *in vivo*. For example, one could use this technique to achieve a therapeutic effect *in vivo* by systemic administration of an adenovirus encoding eNOS, chemically conjugated with anti-ACE mAb 9B9, to enhance eNOS expression in the rat lung and attenuate systemic hypertension in SHR-SP rats.

Further, the Examiner states that although enhanced luciferase activity and expression of carcinoembryonic antigen was detected in the pulmonary endothelium, significant levels of luciferase expression were still detected in liver, spleen, muscle, testis, brain and heart tissues of treated rats. Applicants' would like to respectfully point out to the teachings of their specification which demonstrate that double targeting approach resulted in 27-fold higher gene expression in the lung than in the liver and 8-fold higher expression in the lung than in the spleen. The specification also teaches that this

approach achieved an improvement in relative selectivity for the lung of over 300,000-fold and the lung:spleen ratio improved by > 6000-fold (Figure 3, page 29, line 6 - page 30 line 16). Hence, even though the luciferase expression was detected in other tissues, its expression was significantly lower compared to the lungs.

Accordingly, based on the above-mentioned amendments and remarks, Applicants respectfully request that the rejection of claims 7 and 9-12 under 35 U.S.C 112 be withdrawn.

The 35 U.S.C. §103, Obviousness, Rejection

Amended claims 1 and 3-6 stand rejected under 35 U.S.C. 103(a) as being unpatentable over **Sosnowski et al.** (W098/40508) in view of **Muzykantov et al.** (Am. J. Physiol. 270: L704-L713, 1996) for the same reasons already set forth in the previous Office Action mailed on 11/5/03 (pages 11-14) since the Examiner finds the Applicants respectfully traverse this rejection.

The Examiner contends that **Sosnowski et al.** disclose a tropism-modified adenoviral vector system that specifically targets cells comprising all the elements that are taught by the present invention except the use of a bi-specific antibody conjugate linking a Fab fragment of an anti-Ad5 knob antibody with an anti-angiotensin converting enzyme antibody, more specifically a bi-specific antibody conjugate linking 1D6.14 and 9B9 antibody, in their tropism-modified adenoviral vector system. Additionally, the Examiner further states that **Muzykantov et al.** disclose that the Mab 9B9 to angiotensin converting enzyme is

a safe and specific carrier for drug targeting to the pulmonary endothelium and that it is internalized by endothelial cells both in vitro and in vivo without significant intracellular degradation. Finally, the Examiner states that since the combined teachings of the two cited references make it obvious and motivate an ordinary skilled artisan to carry out the above modification with reasonable expectation of success, the claimed invention as a whole was prima facie obvious in the absence of evidence to the contrary. The Applicants respectfully disagree.

Claim 3 is canceled and Claim 1 is amended to incorporate limitation of claim 3. Claim 4 is amended to change its dependency. Amended claim 1 recites a transductionally and transcriptionally modified adenoviral vector with improved efficacy at the target site and reduced transgene expression at the non-target site *in vivo* comprising a targeting component that comprises a bi-specific antibody conjugate linking a Fab fragment of an anti-Ad5 knob antibody with an anti-angiotensin converting enzyme antibody where the angiotensin converting enzyme molecule is expressed on the target cells and tissue specific promoter that drives the expression of a transgene carried by the vector in the target cells.

Applicants note that **Sosnowski et al**. teach that FGF-2 mediated enhancement in gene expression was due to infection of greater percentage of target cells (page 131, line 17-30). In fact, **Sosnowski et al**. teaches that FGF2-Adenoviral vector induced 12 to 20-fold less transgene expression in the liver than non-retargeted Adenoviral vector (page 163, line 8 – line 10). **Muzykantov et al.** contemplate the use of Mab 9B9 for selective intracellular delivery of drugs to the pulmonary vascular endothelium after systemic administration (abstract).

Neither of the two cited references have contemplated or expressed the need to combine the two different techniques. In fact, based on the teachings and the successes of **Sosnowski et al.** and **Muzykantov et al.**, a person having ordinary skill in this art would simply not be motivated to replace or combine the two techniques taught by the two references.

Further, all the elements of the present invention are not taught by combination of the two references. The adenoviral vector of the present invention comprises of a bi-specific antibody conjugate linking Fab fragment of the anti-Ad5 knob antibody with an anti-angiotensin converting enzyme antibody. Additionally, as is well-known in the art and also discussed in **Sosnowski et al**. (page 28, lines 3-9), any attempt to modify the adenovirus vector should not affect the vector's ability to attach to specific receptors of target cell, get internalized and transfer the gene to the nucleus to be expressed. Hence, just combining the teachings of the two references does not guarantee success in the use of the vector of the present invention.

Applicants assert that obviousness requires that the prior art relied upon fairly teach or suggest all the elements of the instant invention and that an incentive or motivation be present in the prior art to produce the claimed invention with reasonable expectation of success in its production. The Applicants have shown that **Sosnowski et al.** and **Muzykantov et al.** do not teach or suggest all the elements of the present invention, nor do they provide an incentive or motivation to produce the claimed invention with reasonable expectation of success in its production. Hence, the subject matter of the present invention is not obvious

to one with ordinary skill in the art at the time the invention was made. Accordingly, the Applicants request that the rejection of claims 1 and 3-6 under 103(a) be withdrawn.

This is intended to be a complete response to the Office Action mailed March 9, 2004. Applicants submit that the pending claims are in condition for allowance. If any issues remain outstanding, please telephone the undersigned attorney of record for immediate resolution.

Respectfully submitted,

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